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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
VANDERVEGT, FRANCOIS P

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/828,423	HILLMAN ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-21* is/are pending in the application.

4a) Of the above claim(s) *4, 7, 9, 10, 13, 18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,5,6,8,11,12,14-17,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Examiner in charge of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to F. Pierre VanderVegt, Ph.D. in Art Unit 1644.

This application is a continuation of U.S. Application Serial Number 09/388,774, which is a divisional of U.S. Application Serial Number 09/074,579.

Claims 1 and 2 have been canceled.

Claims 3-21 are currently pending.

Claims 4, 7, 9, 10, 13, 18 and 19 stand as withdrawn pursuant to Applicant's election with traverse in the paper filed March 25, 2002.

Claims 3, 5-6, 8, 11-12, 14-17 and 20-21 are the subject of examination in the present Office Action.

Response to Arguments

1. In view of the Appeal Brief filed on October 10, 2003, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

2 In view of the new grounds of rejection presented below, the present Office Action is made **NON-FINAL**.

Specification

3. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: the specification as originally filed does not provide support for the recitation of "a polypeptide having a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1" in claim 1.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 3, 5-6, 8, 11-12, 14-17 and 20-21 are rejected under 35 U.S.C. 101 because the claimed invention lacks a credible asserted utility or a well-established utility.

The claims are most broadly drawn to a antibodies directed to "a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, b) a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, said naturally-occurring amino acid sequence encoding a polypeptide having protease inhibitor activity and c) an immunogenic fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:1."

The polypeptide of SEQ ID NO: 1 and naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 to which the claimed antibodies are directed are not supported by either a specific and substantial asserted utility or a well-established utility. While the specification asserts that the utility of the polypeptides is for "the diagnosis, treatment or prevention of reproductive, developmental, neoplastic and immunological disorders" (page 2, lines 31-33 and page 3, line 1 for example), in order to establish such an asserted utility as substantial or well-established, there must be credible evidence that the polypeptide is of consequence in the conditions being diagnosed or treated. A well established utility is a specific, substantial, and credible utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material. Identifying a DNA segment derived from overlapping cDNAs and determining a function for it's deduced putative polypeptide product based solely on primary polypeptide sequence does not endow the polypeptide with such a utility. Applicant has generated the deduced amino acid sequence of the protein product (SEQ ID NO:1) from a consensus nucleic acid sequence generated via computer alignments using a partial cDNA sequence from Incyte Clone 688183 from the uterus cDNA library and a computer search for amino acid sequence alignments. A consensus nucleic acid sequence (SEQ ID NO: 2) was derived

from overlapping or extended cDNA sequences of 14 clones (page 14, lines 1-17 of the instant specification, for example). Applicant has disclosed this deduced amino acid sequence is a human growth-associated protease inhibitor heavy chain precursor termed by Applicant as GAPIP and has disclosed that this computer generated molecule polypeptide has 28% overall identity to human pre-inter-a-trypsin inhibitor and 27% and 23% identity to human pre-inter-a-trypsin inhibitor heavy chains H1 and H3, respectively (page 14, lines 31-32 and page 15, lines 2-11 for example). The specification states purported uses for the protein including "the diagnosis, treatment or prevention of reproductive, developmental, neoplastic and immunological disorders" (page 2, lines 31-33 and page 3, line 1 for example). However, there is no clear guidance from the specification that their protein would have the same or similar biological properties as human pre-inter-a-trypsin inhibitor because the proposed uses for the claimed computer deduced protein are based solely upon computer alignment with known proteins. Since the claimed protein and the prior art proteins only share 27% sequence identity there would be no predictability that this small sequence identity would render the biological activities of the proposed protein and the known human pre-inter-a-trypsin inhibitor similar because, Applicant has not disclosed whether the biological activity of both proteins resides within the common region(s) or elsewhere within the sequence of the proteins, nor does the specification indicate whether the proteins share conserved active or binding sites. Brenner et al. (Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078; of record), at page 6076, column 2, states that, "Fig. 2 shows one of the many pairs of proteins with very different structures that nonetheless have high levels of identity over considerable aligned regions. Despite the high identity, the raw and the statistical scores for such incorrect matches are typically not significant. The principal reasons percentage identity does so poorly seems to be that it ignores information about gaps and about the conservative or radical nature of residue substitutions. From the PDB90D-B analysis in Fig. 3, we learn that 30% identity is a reliable threshold for this database only for sequence alignments of at least 150 residues." Brenner therefore shows in Fig. 2 that reliance upon high identity alone in many pair wise comparisons is insufficient to relate information about structural and/or functional relatedness and in the analysis of Fig. 3 indicates that information which can be gleaned from sequence identity comparisons is database-specific, not general. The Brenner reference puts further emphasis on the need for structural relationships on page 6074, end of first column in the statement, "Since the discovery that the structures of hemoglobin and myoglobin are very similar though their sequences are not, it has been apparent that comparing structures is a more powerful (if less convenient) way to recognize distant evolutionary relationships than comparing sequences." Therefore, the Brenner reference teaches that sequence identity alone is insufficient to establish functional relationships between proteins, rather it must

be used in concert with structural information to accurately establish relationships between proteins. The instant specification does not provide any information on the structural characteristics of GAPIP, only an assertion of putative N-glycosylation sites, putative phosphorylation sites, a putative signal peptide and putative metal-binding site and that "GAPIP has chemical and structural homology with human pre-inter-a-trypsin inhibitor" (page 14, lines 28-29 for example), but this "structural homology" is based solely on the finding of 28% homology to human pre-inter-a-trypsin inhibitor, and not actual structural determination. According to Brenner, sequence homology must be used in concert with structural information, rather than using one to guess the other. The instant specification does not provide any information about the structure of the predicted GAPIP polypeptide, only sequence identity to the human pre-inter-a-trypsin inhibitor, and for this reason the specification provides insufficient information to enable the artisan to reasonably predict that GAPIP is functionally related to human pre-inter-a-trypsin inhibitor and therefore the specification does not teach the artisan a credible utility for GAPIP.

Because the characteristics of GAPIP are based solely upon sequence identity of the protein with other previously known proteins and not based upon analysis of any actually-produced protein product, no biological activity has been established for GAPIP. As such, further research would be required to identify or reasonably confirm a "real world" context of use, for example, to identify any function of GAPIP and conditions for which GAPIP polypeptides, fragments and "naturally occurring" 90% identical polypeptides would be of diagnostic or therapeutic significance.

Applicant argues in the Appeal Brief filed October 10, 2003 that the GAPIP polypeptide is useful for "toxicology testing" and that this constitutes a "real-world" use of GAPIP (pages 12-14 of the Brief for example). Applicant further argues that the biological role or function of the expressed polypeptide is not required to demonstrate this asserted utility (pages 14-18 for example). The Examiner respectfully disagrees with this assessment. In the first place, it is not clear that GAPIP even constitutes an "expressed polypeptide" as asserted by Applicant. The amino acid sequence of GAPIP was deduced from an nucleic acid sequence derived from overlapping cDNA sequences of 14 clones (page 14, lines 1-17 of the instant specification, for example). Accordingly, no GAPIP protein has actually been "expressed." Further, in order to be useful for toxicology testing, there must be some indication of a condition where a putative toxin or agent would affect expression of GAPIP. However, there is no indication of any type of normal or abnormal expression of GAPIP in a "real-world" context.

Accordingly, without a "real-world" use for the protein, antibodies specific therefore are equally not useful, as basic research such as studying the properties of the product of the polypeptide are not considered substantial and credible utility for the claimed invention. Therefore, the specification does not

fairly disclose a substantial and credible utility for the antibody of the instant claims. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), noting "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 3, 5-6, 8, 11-12, 14-17 and 20-21 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Additionally, even in view of a testable activity for those polypeptides that are "naturally-occurring" variants of SEQ ID NO:1 comprising at least 90% identity over the full length of SEQ ID NO:3, the specification still does not appear to provide sufficient guidance such that the skilled artisan is enabled to make and use an antibody to those polypeptides commensurate in scope with the instant claims.

The specification discloses a single working example of a polypeptide that is naturally-occurring and has at least 90% identity to SEQ ID NO: 1; namely, the polypeptide of SEQ ID NO: 1. Nevertheless, there is insufficient guidance in the specification as-filed to direct a person of skill in the art as to how to make and use antibodies to a polypeptide comprising a "naturally-occurring" amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 even wherein said naturally-occurring amino acid sequence has protease inhibitor activity.

Applicant does not appear to have provided sufficient guidance with respect to "naturally-occurring" polypeptides and how to make and use antibodies to them. Although the specification does provide some general guidance as to how to isolate other nucleic acids related to the nucleic acid encoding SEQ ID NO: 1 (e.g., pages 40-42), it is unpredictable that other "naturally-occurring" polypeptides having protease inhibitor activity and at least 90% amino acid sequence identity to SEQ ID NO: 1 exist.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Applicant does not appear to provide sufficient guidance as to other sources of "naturally-occurring" polypeptides which are at least 90% identical to SEQ ID NO: 1 and have protease inhibitor activity. The state of the art did not recognize other "naturally-occurring" polypeptides that had protease inhibitor activity and were at least 90% identical to SEQ ID NO: 1. Even though the level of skill in the art for isolating "naturally-occurring" polypeptides encoded by nucleic acids related to the nucleic acid encoding SEQ ID NO: 1 may have been high with respect to the techniques employed, skill in the art does not render the existence of a "naturally-occurring" polypeptide predictable.

The presence of a single working example and the failure of the state of the art either at the time of filing or since to recognize other "naturally-occurring" polypeptides at least 90% identical to SEQ ID NO: 1 and having protease inhibitor activity indicates that it was highly unpredictable that additional polypeptides meeting these limitation could be isolated, particularly based on the limited guidance provided in the specification as filed. Unlike the fact pattern of In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) where the presence of a hybridoma producing an antibody having the desired properties among the many hybridomas was predictable, in the instant case it is not predictable that other "naturally-occurring" polypeptides exist. Therefore, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue with respect to other "naturally-occurring" polypeptides other than SEQ ID NO: 1.

Consequently, a person of skill in the art is not enabled to make and use an antibody to a "naturally-occurring" polypeptide at least 90% identical to SEQ ID NO: 1 and having protease inhibitor activity; as encompassed by the full breadth of the claims as currently recited, irrespective of the particular form of the antibody (polyclonal, monoclonal, etc.).

6. Claims 3, 5-6, 8, 11-12, 14-17 and 20-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite as part of the invention an antibody which specifically binds a polypeptide comprising a "naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1" wherein said naturally-occurring amino acid sequence has protease inhibitor activity.

A polypeptide comprising the amino acid sequence of SEQ ID NO:1 is adequately described in the specification as-filed, thereby providing an adequate written description of an antibody which specifically binds the polypeptide of SEQ ID NO:1 or immunogenic fragments thereof.

A polypeptide comprising a "naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1" wherein said naturally-occurring amino acid sequence has nucleotide pyrophosphohydrolase activity is a recitation of a genus of polypeptides for which Applicant has disclosed a single species: the polypeptide of SEQ ID NO:1. The claim recites that the polypeptide to which the antibody binds is "naturally-occurring" and has a testable function of "protease inhibitor activity." The specification does not provide any description regarding the identification and protease inhibitor activity testing of other members of the "naturally-occurring" polypeptide genus related to the nucleic acid encoding SEQ ID NO:1.

However, Applicant does not appear to have provided a description of which polypeptide sequences are "naturally-occurring", even among those polypeptides at least 90% identical to the full length of the sequence of SEQ ID NO: 1. Neither does Applicant appear to have provided a description of how the structure of the polypeptide of SEQ ID NO:1 relates to the structure of other "naturally-occurring" polypeptides which have protease inhibitor activity, even for those polypeptides at least 90% identical to the full length of the sequence of SEQ ID NO: 1. Thus neither the common attributes of the genus nor the identifying attributes of individual species other than SEQ ID NO: 1 appear to have been described.

Additionally, there is not an adequate written description of antibodies to a protein comprising SEQ ID NO: 1 or comprising fragments of SEQ ID NO: 1, as such embodiments embrace additional amino acid sequences which are not disclosed by the instant specification and may be the actual target of antibodies to a protein "comprising" SEQ ID NO: 1.

One of skill in the art would conclude that Applicant was not in possession of the claimed genus of polypeptides comprising a "naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1" wherein said naturally-occurring amino acid sequence has protease inhibitor activity. Since Applicant does not appear to have been in possession of the genus of polypeptides to which the instantly recited antibody specifically binds; Applicant in turn does not appear to be in possession of the genus of antibodies specifically binding these polypeptides.

Therefore, only an antibody to SEQ ID NO: 1 or immunogenic fragments thereof meet the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the

filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00; Alternate Fridays 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
January 12, 2004

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